REMARKS

Claims 34-100 are pending in this application. Claims 91-100 have been withdrawn from the Examiner's consideration and, by this amendment, canceled. Claims 34-90 stand rejected. Claims 34 and 74, the pending independent claims, have been amended. Claims 38, 40, 53, 54, 78, and 80 have been canceled. Claims 101 and 102 have been added. Reconsideration of Claims 34-37, 39, 41-52, 55-77, 79, and 81-90, and allowance of Claims 34-37, 39, 41-52, 55-77, 79, 81-90, 101, and 102 in view of the above amendments and following remarks is respectfully requested.

The Rejection of Claims 34, 35, 37, 43, 47, 48, 50, 53, 66, 68, 70-75, 77-81, and 83-86 Under 35 U.S.C. § 102

Claims 34, 35, 37, 43, 47, 48, 50, 53, 66, 68, 70-75, 77-81, and 83-86 stand rejected under 35 U.S.C. § 102(b) as being anticipated by WO 93/14142. Withdrawal of this rejection is requested for the following reasons.

Claims 34 and 74, the pending independent claims, have been amended to recite that the transport agent is a polycarboxylic acid polymer that is hydrophilic at about pH 7.4 and hydrophobic at pH from about 5.1 to about 5.5.

WO 93/14142 describes a drug delivery system that includes an anti-cancer drug that is covalently coupled to a polymeric carrier attached through a side-chain that is stable in the blood stream, but susceptible to hydrolysis by lysosomal enzymes intracellularly. See Abstract. The side-chain is an enzyme cleavable linkage such as an amino acid sequence. See page 16. The polymeric carrier is a copolymer that can be made from monomers including acrylic acid and methacrylic acid. See, for example, Claim 4.

Applicants submit that the cited reference fails to describe the claimed invention. The cited reference fails to describe a composition or method that is effective in disrupting an

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endosomal membrane. The reference describes a composition (polymeric carrier/side-chain/anti-cancer drug) that enters the cell through pinocytosis. See page 3, lines 14-19. In the lysosomal compartment of the cell, the side-chain is cleaved by lysosomal enzymes thereby releasing the anti-cancer drug. See page 16, lines 7-11. The anti-cancer drug then diffuses through the lysosomal membrane into the cytoplasm. The reference fails to describe a composition that is effective in disrupting the lysosomal membrane, or a method in which the lysosomal membrane is disrupted.

Furthermore, the invention as now claimed recites that the transport agent is a polycarboxylic acid polymer that is hydrophilic at about pH 7.4 and hydrophobic at pH from about 5.1 to about 5.5. The Declaration of Patrick Stayton, enclosed herewith, describes various poly(alkylacrylic acids) and shows that polyacrylic acid and poly(methylacrylic acid) are ineffective in hemolysis at the pH found in endosomes. Accordingly, even if the cited reference described endosomal membrane disruption, which it does not, the polymer carriers described in the reference would not be capable of such membrane disruption.

Because the cited reference fails to describe the claimed invention, the reference is not anticipatory. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 34-43, 47, 50, 53, 57-59, 64-81, and 83-86 Under 35 U.S.C. § 102

Claims 34-43, 47, 50, 53, 57-59, 64-81, and 83-86 stand rejected under 35 U.S.C. § 102 as being anticipated by WO 97/09068. Withdrawal of this rejection is requested for the following reasons.

As noted above, Claims 34 and 74 have been amended.

WO 97/09068 describes a site-specific conjugate that includes a stimuli-responsive polymer coupled to a recognition biomolecule. See Abstract. The cited reference describes drug

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delivery applications at page 52, line 19 through page 54, line 4. The reference describes delivery of a drug into a cell, within an endosome, where the drug is released inside the endosome, where the linkage of the polymer to the drug is labile. See page 53, line 23 through page 54, line 2. The reference refers to Figure 8 as depicting the drug delivery. Referring to Figure 8, in response to stimuli, the site-specific conjugate within the endosome releases drug (D) from the conjugate, and drug (D) diffuses through the endosomal membrane and into the cell's cytosol. Figure 8 illustrates that the endosomal membrane remains intact during this process. The reference fails to describe a composition that is effective in disrupting the lysosomal membrane, or a method in which the lysosomal membrane is disrupted.

Furthermore, the invention as now claimed recites that the transport agent is a polycarboxylic acid polymer that is hydrophilic at about pH 7.4 and hydrophobic at pH from about 5.1 to about 5.5. The reference describes the polymer useful in the site-specific conjugate as including a monomer such as acrylic acid and methacrylic acid. The Declaration of Patrick Stayton, enclosed herewith, describes various poly(alkylacrylic acids) and shows that polyacrylic acid and poly(methylacrylic acid) are ineffective in hemolysis at the pH found in endosomes. Accordingly, even if the cited reference described endosomal membrane disruption, which it does not, the polymer carriers described in the reference would not be capable of such membrane disruption.

Because the cited reference fails to describe the claimed invention, the reference is not anticipatory. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 34, 35, 57-61, 70-74 and 84-86 Under 35 U.S.C. § 102(e)

Claims 34, 35, 57-61, 70-74 and 84-86 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,876,989, issued to Berg. Withdrawal of the rejection is requested for the following reasons.

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As noted above, Claims 34 and 74 have been amended.

The Berg reference describes the transfer of molecules into the cytosol of cells by disrupting endosomal and lysosomal membranes using photodynamic treatment. See column 1, lines 4-6. At column 2, lines 22-33, the reference states that the transfer of molecules into the cytosol is achieved

> by exposing the cell(s) to a photoactivatable compound which is taken up by the cell and will be located in endosomes, lysosomes, or other cellular compartments, conjugated to or separately together with carrier molecules . . . and the molecules to be transported into the cytosol and expose the cells to light of suitable wavelength to activate the photosensitizing compound, such that only the endosomal, lysosomal, or other cellular compartment membranes are ruptured and the molecules released in the cytosol.

The reference fails to describe a carrier molecule that is a polymer.

Because the cited reference fails to describe the claimed invention, the reference is not anticipatory. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 37-39, 43-46, 48, 51, 52, 60-69, 75-79, 81, 82, and 87-90 Under 35 U.S.C. § 103

Claims 37-39, 43-46, 48, 51, 52, 60-69, 75-79, 81, 82, and 87-90 stand rejected under 35 U.S.C. § 103 as being unpatentable over WO 93/14142 or WO 97/09068. Withdrawal of the rejection is requested for the following reasons.

The teachings of the cited references have been noted above. Neither of the cited references describes a composition or method that is effective in disrupting an endosomal membrane. Neither reference teaches, suggests, or provides any motivation to make a composition or employ a method that is effective in disrupting an endosomal membrane. The object of each invention described in these references is attained without endosomal or lysosomal membrane disruption.

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As noted by the Examiner, the cited references describe copolymers obtained from monomers of acrylic acid and methacrylic acid, and that the references do not describe ethylacrylic acid, propylacrylic acid, or butyl acrylic acid. The Examiner concludes that, because ethylacrylic acid, propylacrylic acid, and butylacrylic acid are homologs of methylacrylic acid, these alkylacrylic acid polymers are expected to have the same pH behavior as methylacrylic acid. Applicants enclosed herewith the Declaration of Patrick Stayton, which describes the differences in behavior for polyacrylic acid, poly(methylacrylic acid), poly(ethylacrylic acid), and poly(propylacrylic acid). The declaration demonstrates that the pH behavior of polyacrylic acid and poly(methylacrylic acid) is dramatically different from that of poly(ethylacrylic acid) and poly(propylacrylic acid). The declaration also demonstrates that the behavior of poly(ethylacrylic acid) is different from that of poly(propylacrylic acid). The declaration shows that while poly(methylacrylic acid) (and also polyacrylic acid) does not exhibit an effect over the pH range from about 5 to about 7.4, each of poly(ethylacrylic acid) and poly(propylacrylic acid) do exhibit an effect. Because the noted poly(alkylacrylic acids) have properties that are different from the acrylic acid polymers of the cited references, the teachings of the cited references fail to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed invention, which recites a transport agent that is a polycarboxylic acid polymer that is hydrophilic at about pH 7.4 and hydrophobic at pH from about 5.1 to about 5.5.

The cited references, either alone or in combination, fail to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed invention. Withdrawal of the rejection is respectfully requested.

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The Rejection of Claims 60-63 Under 35 U.S.C. § 103

Claims 60-63 stand rejected under 35 U.S.C. § 103 as being unpatentable over WO 93/14142 or WO 97/09068 in view of U.S. Patent No. 5,876,989, issued to Berg. Withdrawal of the rejection is requested for the following reasons.

Claims 60-63 depend from Claim 34, which has been amended.

The deficiencies of the teachings of WO 93/14142 or WO 97/09068 are not cured by the teaching of the Berg reference. Neither WO 93/14142 or WO 97/09068 teaches or suggests a composition that is effective in disrupting the endosomal membrane, or a method in which the endosomal membrane is disrupted. The Berg reference fails to teach or suggest a composition or method that includes a polymer carrier. None of the cited references describes a composition or method that includes a polycarboxylic acid polymer that is hydrophilic at about pH 7.4 and hydrophobic at pH from about 5.1 to about 5.5, as in the claimed invention.

The cited references, either alone or in combination, fail to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed. Withdrawal of the rejection is respectfully requested.

The Rejection of Claim 36 Under 35 U.S.C. § 103

Claim 36 stands rejected under 35 U.S.C. § 103 as being unpatentable over WO 93/14142 or WO 97/09068 in view of U.S. Patent No. 5,807,306, issued to Shapland. Claim 36 depends from Claim 34, which has been amended. Withdrawal of the rejection is requested for the following reasons.

The deficiencies of the teachings of WO 93/14142 or WO 97/09068 are not cured by the teaching of the Shapland reference. Neither WO 93/14142, WO 97/09068, or the Shapland reference teaches or suggests a composition that is effective in disrupting the endosomal membrane, or a method in which the endosomal membrane is disrupted. None of the cited

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references describes a composition or method that includes a polycarboxylic acid polymer that is hydrophilic at about pH 7.4 and hydrophobic at pH from about 5.1 to about 5.5, as in the claimed invention.

The cited references, either alone or in combination, fail to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 53-56 Under 35 U.S.C. § 103

Claims 53-56 stand rejected under 35 U.S.C. § 103 as being unpatentable over WO 93/14142 or WO 97/09068 in view of the Anderson reference (*Bioconjugate Chemistry*, *4*, pp. 10-18, 1993).

The deficiencies of the teachings of WO 93/14142 or WO 97/09068 are not cured by the teaching of the Anderson reference. Neither WO 93/14142 or WO 97/09068 teaches or suggests a composition that is effective in disrupting the endosomal membrane, or a method in which the endosomal membrane is disrupted. None of the cited references describes a composition or method that includes a polycarboxylic acid polymer that is hydrophilic at about pH 7.4 and hydrophobic at pH from about 5.1 to about 5.5, as in the claimed invention.

The cited references, either alone or in combination, fail to teach, suggest, provide any motivation to make, or otherwise render obvious the invention as now claimed. Withdrawal of the rejection is respectfully requested.

New Claims 101 and 102

Claims 101 and 102 have been added. Claims 101 and 102 are similar to Claims 34 and 74, respectively, except that Claims 101 and 102 recite that the transport agent is a poly(alkylacrylic acid) selected from the group consisting of poly(ethylacrylic acid), poly(propylacrylic acid), poly(butylacrylic acid), and mixtures thereof.

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Conclusion

In view of the above amendments and foregoing remarks, applicants believe that Claims 34-37, 39, 41-52, 55-77, 79, 81-90, 101, and 102 are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at (206) 695-1755.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE MARCH 10, 2003

In the Claims:

Claims 34 and 74 have been amended as follows:

34. (Amended) A method for delivering a therapeutic or diagnostic agent to a cell, comprising:

(a) treating a cell with a combination of a transport agent and a therapeutic or diagnostic agent, wherein the combination is taken into the cell by endocytosis to provide an endosome having an endosomal membrane and containing the combination, wherein the transport agent is effective in disrupting the endosomal membrane, and wherein [when the transport agent is a peptide, the therapeutic agent is not a nucleic acid or a peptide] the transport agent comprises a polycarboxylic acid polymer that is hydrophilic at about pH 7.4 and hydrophobic at pH from about 5.1 to about 5.5; and

(b) releasing the therapeutic or diagnostic agent from the endosome into the cell cytoplasm by the action of the transport agent on the endosomal membrane.

74. (Amended) A composition for delivering a therapeutic or diagnostic agent to a cell, comprising a combination of (a) a transport agent and (b) a therapeutic or diagnostic agent, wherein the transport agent is effective in disrupting the endosomal membrane, and wherein [when the transport agent is a peptide, the therapeutic agent is not a nucleic acid or a peptide] the transport agent comprises a polycarboxylic acid polymer that is hydrophilic at about pH 7.4 and hydrophobic at pH from about 5.1 to about 5.5.

Claims 38, 40, 53, 54, 78, 80, and 91-100 have been canceled.

Claims 101 and 102 have been added.

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